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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.           | CONFIRMATION NO. |
|--|-------------|----------------------|-------------------------------|------------------|
| 09/989,279   | 11/19/2001  | Avi J. Ashkenazi     | P2730P1C56                    | 2527             |
| 35489  | 7590        | 05/06/2005           |                               |                  |
| HELLER EHRMAN LLP<br>275 MIDDLEFIELD ROAD<br>MENLO PARK, CA 94025-3506 |             |                      | EXAMINER<br>SPECTOR, LORRAINE |                  |
|  |             |                      | ART UNIT                      | PAPER NUMBER     |
|  |             |                      | 1647                          |                  |

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/989,279

Applicant(s)

ASHKENAZI ET AL.

Examiner

Lorraine Spector, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 119-126, 129-131 and 135-145 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 124-126 and 129-131 is/are allowed.
- 6) ☒ Claim(s) 119-123, 135-145 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 02/6/2004
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

**Part III: Detailed Office Action**

Claims 119-126, 129-131, and 135-145 are pending and under consideration.

The rejection of claims 119-138 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendments.

The rejection of claims 119-124, 127-128 and 132-138 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid of SEQ ID NO: 228 or fragments of such that are usable as hybridization probes, or nucleic acids which encode the protein of SEQ ID NO: 229 or fragments thereof that are useful for making antibodies or have chondrocyte redifferentiation activity, does not reasonably provide enablement for nucleic acids 80, 85, 90, 95 or 99% identical to such, nor which encode a protein 80, 85, 90, 95 or 99% identical to the protein of SEQ ID NO: 400, nor nucleic acids which hybridize to any of the above is withdrawn in view of applicants amendments.

The rejection of claims 119-124, 126-128 and 132-138 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of applicants amendments.

The rejection of claims 119-124 and 131-138 under 35 U.S.C. 112, first paragraph (deposit requirement) is withdrawn in view of applicants amendments.

**Formal Matters:**

The new title of the invention is acknowledged.

**Claim Objections:**

Newly introduced claim 139 is objected to for using the singular "nucleotide" in line two of the claim. Amendment to read --nucleotides-- would be remedial.

**Priority Determination:**

The utility for the claimed nucleic acids is based upon the example that begins at page 530 of the specification, in which it is shown that the polypeptide encoded by the protein is active in a chondrocyte redifferentiation assay. Applicants have provided a copy of that portion of the PCT application which contains the chondrocyte redifferentiation assay. Accordingly, priority is granted to 3/3/00.

It is further noted that applicants may argue that the results of the assay beginning at page 546 of the specification, the delta Ct assay, establish utility and enablement for the claimed invention, resulting in an earlier priority date. That assay is not found to be enabling as required by 35 U.S.C. §112, first paragraph. The results indicate a *mild* amplification in fewer than half the Lung adenocarcinoma, lung squamous cell carcinoma, and colon adenocarcinoma cell lines studied. PRO1111 was found to be amplified approximately two-three fold in 6 of 12 human lung tumor squamous cell carcinoma cell lines, 4 of 11 human lung tumor adenocarcinoma cell lines, and 4 of 17 colon adenocarcinoma cell lines. The finding that the nucleic acid encoding PRO1111 is amplified, likely indicating aneuploidy, in the aforementioned tumor types is insufficient to confer utility or enablement to the nucleic acid. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. In this case, the sequence of PRO1111 was found at no more than three copies per cell, and only in a minority of tumors tested. The person of ordinary skill in the art would not consider the results to be significant or diagnostic in view of the review by Sen. Further, a search of the art has revealed that J. Wang et al. have reported that the protein encoded by SEQ ID NO: 228 is *down regulated* in brain tumor (see search results for us-09-989-2749-229.rspt, result 1, enclosed). Accordingly, it is not clear whether or not PRO1111 is diagnostic of cancer, or if so which cancers, and the specification does not enable the use of PRO1111 for such diagnosis, and the result from the amplification assay cannot be relied upon to establish a priority date.

Applicants have traversed this finding, largely by reference to the Ashkenazi declaration.

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The declaration by Dr. Ashkenazi under 37 CFR 1.132 filed 12/6/2004 is insufficient to establish enablement for the gene amplification assay because:

In the Ashkenazi Declaration filed under 37 CFR 1.132 (dated 9/15/2003 and filed 12/6/2004), Declarant argues that "detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes." This argument is not persuasive, as in the instant case it has not been established that the changes in the amount of DNA were significant. They occurred in only a minority of samples of the particular cancer types, and cannot be considered to be diagnostic in the absence of significance, that is a statistically significant correlation between increased copy number and cancer. It remains that random aneuploidy is the most parsimonious explanation of the results in the specification.

Declarant also argues that even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not enabled, and priority stands at 3/3/2000.

**Rejections Over Prior Art:**

Priority is set at 3/3/00.

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A search of the nucleic acid sequence databases revealed the following prior art:

| Reference                                      | Date     | Author   | Identity to SEQ ID NO:228  |
|--|----------|----------|--|
| AI769814                                       | 12/21/99 | NCI-CGAP | 100% to bases 1703-2180  |
| U.S. Patent Number<br>6,689,866, SEQ ID NO: 9  | 3/8/00   | Shimkets | 99.7% to bases 1-2183  |
| U.S. Patent Number<br>6,689,866, SEQ ID NO: 31 | 3/8/00   | Shimkets | Encodes XC domain, 100% identity to<br>SEQ ID NO : 229, residues 45-492. |

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-123 and 135-145 are rejected under 35 U.S.C. 102(a) as being anticipated by Locus AI769814.

The teachings of the reference are summarized above. The reference sequence is 100% identical over its entire length to SEQ ID NO: 228. The reference is silent with respect to whether or not the nucleic acid encodes a protein with chondrocyte redifferentiation activity. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

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Claims 119-123 and 135-145 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 1 of the publication is 99.8% identical to SEQ ID NO: 228 of the instant application, at bases 1-2184 (bases 160-2342 of the publication). Fragments within the metes and bounds of claims 139-145 are disclosed at pages 2-4. Accordingly, the claims are anticipated by Jacobs. Applicants argument pertaining to the filing date has been addressed and is found not to be persuasive, above.

Claims 119-123, and 135-145 are rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins, and antibodies, and the '532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent). SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Vectors and host cells are discussed at columns 37-38. Accordingly, the claims are anticipated by Shimkets. Applicants argument pertaining to the filing date has been addressed and is found not to be persuasive, above.

**Advisory Information:**

Claims 124-126 and 129-131 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

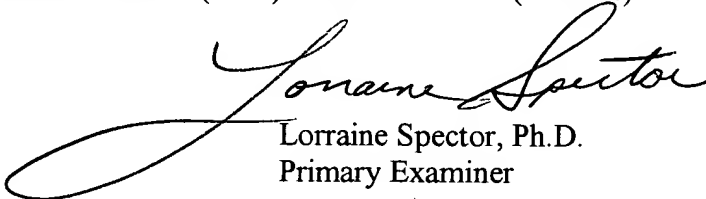
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.  
Primary Examiner

5/4/05